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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/559,878

12/07/2005

Harry John Wadsworth

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07/06/2009

GE HEALTHCARE, INC.

IP DEPARTMENT 101 CARNEGIE CENTER

PRINCETON, NJ 08540-6231

EXAMINER

BALASUBRAMANIAN, VENKATARAMAN

ART UNIT

PAPER NUMBER

1624

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DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/559,878	Applicant(s) WADSWORTH ET AL.	
	Examiner /Venkataraman Balasubramanian/	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 April 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4-7 and 9-28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4-7 and 9-28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/6/2009 has been entered. Claims 1, 4-7 and 9-28 are pending.

Interview Summary

A telephonic interview was held on June 23, 2009 as requested by applicants' representative Craig Bohken. Both the 112 first paragraph scope of enablement rejection and 103 rejection over Grushin were discussed. Examiner restated the reasons for these rejections. No agreement was reached.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-7 and 9-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for fluoridation of diphenyliodonium salt, phenyliodonium salt bearing unsubstituted acetophenone as well as methyl and methoxy substituted acetophenone, does not reasonably provide enablement for any or all iodonium salt and fluoridation any or all aromatic or heteroaromatic compounds

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generically embraced in claim 1 and compounds with diverse structure embraced in claims 15-18. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following apply:

In evaluating the enablement question, following factors are considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. The nature of the invention and the state of the prior art:

The invention is drawn to production of aromatic or heteroaromatic fluorine labeled compound by fluoridation of iodonium salt with fluoride in a solvent comprising water. Specification is not adequately enabled for fluoridation of any or all iodonium salt and fluoridation of any or all aromatic or heteroaromatic compounds including those with various reactive functional groups which may be susceptible to the reactions embraced in the process generically embraced in claim 1 and compounds with diverse structure embraced in claims 15-18.

Instant claims recites fluoridation of any iodonium salt but the nucleophilic displacement can occur on both sides of the iodonium salts and if these groups are not aromatic and heteroaromatic, the reaction will not lead to desired product namely fluorinated aryl or heteroaryl. There is no showing in the specification how to one make

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fluorinated aryl or heteroaryl with such starting materials. Even if one of the group is aryl or heteroaryl there is no guarantee that the reaction would occur to yield fluorinated aryl or heteroaryl. Specification is silent about how to perform the reaction in such cases and arrive at the desired product. In addition, as recited the starting iodonium salt is permitted to be any compound thereby permitting variously substituted iodonium salts. Such a recitation would not exclude reactive groups which may also participate in the said fluoridation reaction. Specification offers no teachings or suggestion as to how to perform the process of claim 1 in presence of these reactive groups. Specification has no teaching or suggestion as how to make the starting material for the said fluoridation with any substituents including reactive groups. The same is true for the compounds shown in claim 15 and claim 17. There is no teaching of how fluoridation of such compounds is achieved and what starting material is used. Specification offers no teachings or suggestion as to how to perform the process of claim 1 for making these compounds. Note US 2006/0292060 (apparently instant applicants) states:

The use of this reaction in the radiofluoridation of iodonium salts has been reported by Pike et al [1995 J Chem Soc Chem Comm pp2215-16] although with variable radiochemical yield (ROY). The reason for the variability in RCY was not understood. Subsequent reports from the same group [Shah et al 1998 J Chem Soc (Perkin Trans 1) 25 pp2043-6 and Martin-Santamaria et al 2000 Chem Comm pp649-50] do not offer any further explanation for the variable RCY: More recently, Wust et al [2001 J Labelled Compd Radiopharm 44 ps12-3] reported that the reaction of phenyliodonium tosylate with [¹⁸F] potassium fluoride (in the presence of Kryptofix TM)

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yielded a very low amount of the desired [18F] corticosteroid. Furthermore, the present applicants have found that radiofluoridation of iodonium salts according to the methods described above produces 5 highly variable RCY (5% to 40%) of the desired [¹⁸F] aryl fluoride product. Such lack of reproducibility makes the use of iodonium salts for the synthesis of [18F] aryl fluorides problematic.

Thus, it clear that the fluoridation process is a specialized art with certain degree of unpredictability. A process which viable for one starting material need not do so for others. Hence, specification should teach or suggest how to make such compounds with varying structural cores and substituents. Presence of reactive groups would be chemically incompatible the process of fluoridation embraced in the instant claims. Also, note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.". Clearly that is the case here.

2. The predictability or lack thereof in the art:

Hence the process as applied to the above-mentioned compounds claimed by the applicant is not an art-recognized process and hence there should be adequate enabling disclosure in the specification with working example(s).

4. The amount of direction or guidance present: Examples illustrated in the experimental section or written description offer no guidance or teachings as to how perform the process of claim 1 when reactive substituents or chemically incompatible substituents are present in the starting material.

5. The presence or absence of working examples:

Although examples in specification show the fluoridation process, they are limited to compound with no reactive functionality. There are no representative examples showing the viability of the process for plurality of reactive substituents embraced in the instant claims.

6. The breadth of the claims:

Specification has no support, as noted above, for all compounds generically embraced in the claim language would lead to desired compound of formula I with said reactive groups and there is also no valid chemical reasoning for one trained in the art to expect that all these functional groups would be inert toward the halogenating agent embraced in the process claim.

7. The quantity of experimentation needed:

The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired structure, namely compound of formula I embraced in the instant claims.

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of reactant- reagent interactions in general, and the lack of working examples regarding the viability of the claimed compounds and

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processes of making embraced in the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

This rejection is same as made in the previous office action but now limited to currently pending claims.

Applicants' traversal is not persuasive. As recited, applicants' claims are reach through claims. Based on the fluoridation of diphenyliodonium salt, phenyliodonium salt bearing unsubstituted acetophenone as well as methyl and methoxy substituted acetophenone, instant claims reach through for fluoridation of any or all iodonium salt and fluoridation any or all aromatic or heteroaromatic compounds which are electron deficient.

Applicants have argued that instant Q is now defined as electron deficient aryl or hereroaryl. Contrary to applicants' urging, the choice of Q includes both electron deficient and electron rich groups. For example, alkyl, O-alkyl, cycloalkyl and many such groups embraced in the choice of Q are not electron deficient groups. Note also the

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choice of R¹-R⁵ includes such groups and therefore there the nucleophilic attack can give both products, Q-F and Aryl-F.

As noted above, the radio fluorination is specialized art and applicants have also provided Welch as evidence to that. The examples shown in the specification is limited to simple compounds and not for the diverse compounds claimed generically and more specifically in claims 15 and 17. Hence, these examples cannot be deemed as objective enablement as the species and genus recited are various largely and each required a distinct process for making the intermediates and there is no guarantee that fluoridation would work on all of them. Furthermore, the radiofluorination is specialized art and required guidance. A radiolabelled material is distinct form unlabelled material. Hence, species claimed in claims 15 and 17 require support in specification.

Hence, this rejection is proper and is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 4-7 and 9-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grushin et al.

Grushin et al. teaches a process for fluorination using biphasic system containing water . See entire document especially page 2131.

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Instant claims differ from the reference in requiring a water alone or water and miscible solvent for the said reaction.

While Grushin did not teach such a combination of solvent for the said fluoridation reaction, Grushin clearly teaches that for the arylation anions by diphenylhalonium salts use of homogeneous solvent system with water, aqueous alcohols, acetone, dioxane etc. See first paragraph, page 2130.

Thus, one having ordinary skill in the art at the time of the invention was made would have been motivated to combine teachings of the references and employ the process taught by the prior art to the starting materials and reactants of the instant invention and expect to obtain the desired product because he would have expected the analogous starting materials and reactants react similarly in view of the combine teaching of the prior art. It has been held that application of an old process to an analogous material to obtain a result consistent with the teachings of the art would have been obvious to one having ordinary skill. Note *In re Kerkhoven* 205 USPQ 1069.

See also MPEP 2144.05, which says, under Optimization Within Prior Art Conditions or Through Routine Experimentation:

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature

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between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%). See also *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

This rejection is same as made in the previous office action but limited to claims 1, 4-7 and 9-15.

Applicants' argument to overcome this rejection is not persuasive. Grishin clearly teaches that water can be used for such reactions and it is well within skill set of one trained in the art to modify the solvent system as and when required for each starting material and reagents. Applicants' amendment to claim 1 to recite 100% water and water with water miscible solvent does not overcome this rejection. As noted above Grishin teaches fluoridation reaction in water and chloroform thereby teaches that water is not detrimental to the progress of the reaction. Furthermore, Grishin also teaches that nucleophilic displacement reaction of several diphenyliodonium salts with various nucleophiles in both water miscible and water immiscible solvents. See Table 1.

Hence, it would be obvious to one trained in the art to use water as solvent for fluoridation reaction including 100% water and water in water miscible solvent for reaction by appropriate optimization.

Also see *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007), wherein the court stated that

[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Such is the case with instant claims. Grushin teaches use of water and chloroform for fluoridation and also teaches use of water miscible and water immiscible solvents along with water for such nucleophilic displacement reactions. Hence, one trained in the art would be motivated to make fluoroaryl and fluoroheteroaryl compounds using the process of Grushin with water and water- with water miscible solvents . Such a know-how is within the skill set of one trained in the art.

Applicants have not provided any comparative data showing unexpected superior results. Even then, with fluoridation of large diverse compounds claimed, it is not possible to assert the genus as a whole would behave the same manner given the prior art results stated in the instant specification. Note *Ex parte Gelles* 22 USPQ 2nd 1318, especially the following quote: " The evidence relied upon also should be reasonably

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commensurate in scope with the subject matter claimed and illustrate the claimed subject matter " as a class" relative to prior art subject matter."

Hence, this rejection is proper and is maintained.

Claims 1, 4-7 and 9-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grushin et al. and Shah et al (Journal of Chemical Society, Perkin Transactions 1, 1998, 13, pp 2043-2046) and further in view of Chen et al. (Synlett, 2000, No8, 1175-1177).

Grushin et al. teaches a process for fluorination using biphasic system containing water . See entire document especially page 2131. Furthermore, Grushin teaches both water immiscible and water miscible solvents along with water for such nucleophilic reactions as discussed in the above 103 reaction.

Claims 16-28 relate to radiolabeling with ^{18}F . Claim 10 relates to use of solid support.

Shah et al. teach preparation of fluoride-labeled aromatics using aryl iodonium salts as aryl bearing reagent and CsF or APE KF (same as Kryptofix, claim 5) as a source of fluoride (see Tables 1 and 2 on page 2044). Shah et al. describe their method having utility in preparation of fluorinated DOPA (see page 2-43, column 1, structure 1). The fluorine attached to the ring in Shah et al is an ^{18}F isotope (see page 2044, column 1, scheme 4). The product is purified via HPLC (page 2045, column 1, lines 4-7).

Chen et al teach preparation and utility of solid supported arylodonium salts.

One skilled in the arts would find it obvious to combine the process taught by Grushin with Shah and Chen and utilize the process for not only making fluoroaryl and

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heteroaryl compounds but also ^{18}F -labeled compounds including using solid support to perform the reaction of Grushin and Shah et al. It has been held that application of an old process to an analogous material to obtain a result consistent with the teachings of the art would have been obvious to one having ordinary skill. Note *In re Kerkhoven* 205 USPQ 1069.

Also see *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007), wherein the court stated that

[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Such is the case with instant claims. Grushin teaches use of water and chloroform for fluoridation and also teaches use of water miscible and water immiscible solvents along with water for such nucleophilic displacement reactions. Hence, one trained in the art would be motivated to make fluoroaryl and fluoroheteroaryl compounds using the process of Grushin with water and water with water miscible solvents. Such a know-how is within the skill set of one trained in the art. In addition one trained in the art would be motivated to combine the teachings of Grushin with that of Shah and Chen teaching and apply such a process for ^{18}F -labeling with or without the use of solid support.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

/Venkataraman Balasubramanian/

Primary Examiner, Art Unit 1624

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